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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/603,663 06/23/00 ZHU

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021971- HM12/1010  
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EXAMINER

PRASTHOFFER, T

ART UNIT

PAPER NUMBER

1627  
DATE MAILED:

10/10/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

**Office Action Summary**

Application No.

09/603,663

Applicant(s)

ZHU ET AL.

Examiner

Thomas W Prasthofer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 June 2001.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-9, 14, 18-24 and 36-45 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9, 14, 18-24 and 36-45 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **Detailed Action**

### **Status of the Application**

Receipt is acknowledged of a response to an office action on June 27, 2001 in Paper No. 8.

### **Status of the Claims**

Claims 10-13, 15-17, and 25-35 were cancelled and new claims 36-45 were added in Paper No. 8.

Claims 1-9, 14, 18-24, and 36-45 are pending in the present application and are being examined on their merits.

### **Withdrawn Objections/Rejections**

1. The objection to claim 14 in the office action mailed February 27, 2001 (Paper No. 6) are withdrawn in response to applicant's cancellation of claim 14.
2. The rejections of claims 1-24 under 35 U.S.C. 101 and the associated rejection under 35 U.S.C. 112, first paragraph in ¶ 7 and 8 of Paper No. 6 are withdrawn in response to applicant's arguments.
3. The rejections of claims 2-4 under 35 U.S.C. 112, second paragraph in ¶s 9-11 of Paper No. 6 are withdrawn in response to applicant's amendment.
4. The rejections of claims 10-13, 15, and 16 under 35 U.S.C. 112, second paragraph in ¶s 12-17, 20, and 21 of Paper No. 6 are withdrawn in response to applicant's cancellation of these claims.

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5. The rejections of claim 14 and 18 under 35 U.S.C. 112, second paragraph in ¶s 18, 19 and 22-25 of Paper No. 6 are withdrawn in response to applicant's amendment.
6. The rejection of claims 1-4, 10-17, 20, 21, and 24 under 35 U.S.C. 102(a) in ¶ 26 of Paper No. 6 is withdrawn in response to applicant's amendment.
7. The rejection of claims 1-12, 20, and 24 under 35 U.S.C. 103(a) in ¶ 27 of Paper No. 6 is withdrawn in response to applicant's amendment.

**New Grounds of Rejection**  
(Necessitated by Applicant's Amendment)

**New Grounds of Rejection – 35 U.S.C. 112, first paragraph**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 2, 22, and 36-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (New Matter).

Applicant amended claims 1, 2, and 22 and added new claims 36-45 in Paper No. 8. Applicant has not indicated where support for these amendments and new claims can be found in the specification. Applicant may overcome this rejection by specifically pointing out support for any amendment made to the disclosure in accordance with MPEP 714.02.

**New Grounds of Rejection – 35 U.S.C. 112, second paragraph**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 41 recites the limitation "the transcription factor" in lines 9. There is insufficient antecedent basis for this limitation in the claim.

B. Claim 41 recites the limitation "the first polypeptide subunit" in line 11. There is insufficient antecedent basis for this limitation in the claim.

C. Claim 41 recites the limitation "the second polypeptide subunit" in line 11. There is insufficient antecedent basis for this limitation in the claim.

D. Claim 41 recites the limitation "the reporter gene" in line 21. There is insufficient antecedent basis for this limitation in the claim.

E. Claim 44 recites the limitation "the transcription factor" in lines 9. There is insufficient antecedent basis for this limitation in the claim.

F. Claim 44 recites the limitation "the reporter gene" inline 21. There is insufficient antecedent basis for this limitation in the claim.

G. Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: method steps that would assay the library of mutagenized vectors for improved binding affinity.

**New Grounds of Rejection – 35 U.S.C. 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 1-9, 14, 20-24, and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nandabalan et al. (May, 2000, filed June 13, 1997) U.S. Patent No. 6,057,101, Hoeffler et al. (1999, WO 99/28502), and Hua et al. (1997) Plasmid 38:91-96.

The Nandabalan reference teaches methods for detecting protein-protein interactions that include expressing a library of tester fusion proteins and a target fusion protein in yeast cells and selecting those yeast cells in which a reporter gene is expressed, see, for example, "SUMMARY OF THE INVENTION" columns 4 and 5 (reads on the corresponding method steps of claim 1). Single chain antibody (sFv) libraries are taught on pages 4 and 8 (reads on present claim 14 except for independently variable first and second polypeptide subunits). The yeast two-hybrid system is taught on pages 10-11.

The Nandabalan reference teaches transforming the library of tester expression vectors into yeast cells which contain a reporter construct, see, for example, "SUMMARY OF THE INVENTION" columns 4 and 5 (reads on the corresponding method step of current claim 2). The 1<sup>st</sup> and 2<sup>nd</sup> transcription sequences encoding the activation and DNA binding domains of a transcription activator read on the corresponding domains in current claims 2 and 3.

Columns 4 and 5 also teach a tester fusion protein vector comprising sequences that encode one domain of the transcription activator and a tester protein, a target fusion protein vector comprising sequences that encode one domain of the transcription activator and a target protein, a 1<sup>st</sup> population of haploid yeast cells containing a library of tester expression vectors, and a 2<sup>nd</sup> population of haploid yeast cells containing a target expression vector (reads on current claim 4). The same sections also teach mating of haploid yeast cells of opposite mating types and  $\alpha$  and  $a$  type strains of yeast (reads on current claims 5 and 6).

Figure 6 and column 9, lines 34-43 of the reference teach target fusion proteins associated with disease states including cancer (reads on current claim 20) as well as hormone receptors (page 36). According to figure 3 and column 17, lines 45-55, the reporter gene is selected from a group including but not limited to  $\beta$ -galactosidase, chloramphenicol acetyl

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transferase (CAT), luciferase, or green fluorescence protein (reads on current claim 24). Human-derived sFvs are taught on page 52 (reads on new claim 36). Page 23 teaches the heavy and light chain variable domains in either order from N to C terminus in fusion proteins (reads on new claims 37, 38, and 40).

The Nandabalan reference does not explicitly teach libraries containing two independently varying subunits fused with a transcriptional regulator, library diversity greater than  $1 \times 10^8$ ,  $1 \times 10^{10}$  or  $1 \times 10^{12}$  (claims 7-9 as amended), or human growth factor receptor as a target protein.

The Hoeffler et al. reference teaches a method of screening for protein-protein interactions using yeast expression vectors encoding libraries of single chain antibodies. The expression vectors comprise a first nucleotide sequence encoding either  $V_H$  or  $V_L$  subunit, a second nucleotide sequence encoding either  $V_L$  or  $V_H$  subunit, and a peptide linker that connects the two subunits (see, for example, page 5, lines 1-16, page 7, lines 10-13, and figure 4). The single chain antibody libraries are comprehensive populations of  $V_L$  and  $V_H$  subunits (vary independently from one another) linked by short, flexible peptide linkers (page 8, lines 16-17). The reference presents an invention that can probe an animal's entire repertoire of  $> 10^{12}$  combinations of light and heavy variable chains (page 11, lines 12-15, 21-22, and 25). The Hoeffler et al. reference states that there is a limitation to the diversity of libraries made that is imposed by transformation efficiency not much greater than  $10^7$ . The reference in no way implies that libraries of greater diversity are not desired. The yeast strains used can be diploid or haploid and may be mated (page 22, lines 21-24). The use of  $\alpha$  and  $a$  strains of haploid yeast for mating is the most common method of yeast mating. The source of DNA for generating the single chain antibody expression vectors may be from immunized or non-immunized animals including humans and mice and from tissues including spleen cells and lymphoblastoid cells (page 32, lines 5-10). Vectors encoding activating or DNA binding domains of transcriptional activators are taught on page 5. Transcriptional activators such as GAL4 are taught on page 12.

It would have been obvious to anyone of ordinary skill in the art at the time that the invention was made to use the two-hybrid assay system of Nandabalan et al. with the single chain antibody expression library of Hoeffler et al. Motivation for this combination is found in the Hoeffler et al. reference on pages 1-4 and 37-43. The screening of single chain antibodies in

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the two-hybrid expression system allows the rapid identification of antibody-antigen pairs. This motivation extends to the screening of any two-subunit proteins, such as receptors and transcription factors in which altering the combinations of subunits produces molecules with different functions.

The Hua et al. reference teaches an homologous recombination method for cloning in yeast. The reference teaches that:

*“Functional analysis of a new gene usually involves many molecular biological technologies, including...yeast two hybrid systems for studying protein-protein interactions. These technologies involve many steps of DNA manipulation and are rather time-consuming. Simplifying the cloning process would increase research efficiency and reduce the cost of investigation.”* (page 91, column 1)

Here the Hua et al. reference provides motivation for one of ordinary skill in the art to apply the method of homologous recombination to large scale screenings of protein-protein interactions (such as antibody-antigen or scFv-antigen interactions). The limitation with respect to transformation efficiency cited in the Hoeffler et al. reference does not apply to the Hua et al. method. One would have had reasonable expectation for success because no new methods or reagents would be required and the methods employed had all been demonstrated to be operable.

11. Claims 1-9, 14, 20-24, and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nandabalan et al. (May, 2000, filed June 13, 1997) U.S. Patent No. 6,057,101, Hoeffler et al. (1999, WO 99/28502), and Gietz et al. (1995) Methods in Molecular and Cellular Biology 7(3) 254-269.

The Nandabalan reference teaches methods for detecting protein-protein interactions that include expressing a library of tester fusion proteins and a target fusion protein in yeast cells and selecting those yeast cells in which a reporter gene is expressed, see, for example, “SUMMARY OF THE INVENTION” columns 4 and 5 (reads on the corresponding method steps of claim 1). Single chain antibody (scFv) libraries are taught on pages 4 and 8 (reads on present claim 14



except for independently variable first and second polypeptide subunits). The yeast two-hybrid system is taught on pages 10-11.

The Nandabalan reference teaches transforming the library of tester expression vectors into yeast cells which contain a reporter construct, see, for example, "SUMMARY OF THE INVENTION" columns 4 and 5 (reads on the corresponding method step of current claim 2). The 1<sup>st</sup> and 2<sup>nd</sup> transcription sequences encoding the activation and DNA binding domains of a transcription activator read on the corresponding domains in current claims 2 and 3.

Columns 4 and 5 also teach a tester fusion protein vector comprising sequences that encode one domain of the transcription activator and a tester protein, a target fusion protein vector comprising sequences that encode one domain of the transcription activator and a target protein, a 1<sup>st</sup> population of haploid yeast cells containing a library of tester expression vectors, and a 2<sup>nd</sup> population of haploid yeast cells containing a target expression vector (reads on current claim 4). The same sections also teach mating of haploid yeast cells of opposite mating types and  $\alpha$  and  $a$  type strains of yeast (reads on current claims 5 and 6).

Figure 6 and column 9, lines 34-43 of the reference teach target fusion proteins associated with disease states including cancer (reads on current claim 20) as well as hormone receptors (page 36). According to figure 3 and column 17, lines 45-55, the reporter gene is selected from a group including but not limited to  $\beta$ -galactosidase, chloramphenicol acetyl transferase (CAT), luciferase, or green fluorescence protein (reads on current claim 24). Human-derived sFvs are taught on page 52 (reads on new claim 36). Page 23 teaches the heavy and light chain variable domains in either order from N to C terminus in fusion proteins (reads on new claims 37, 38, and 40).

The Nandabalan reference does not explicitly teach libraries containing two independently varying subunits fused with a transcriptional regulator or library diversity greater than  $1 \times 10^8$ ,  $1 \times 10^{10}$  or  $1 \times 10^{12}$  (claims 7-9 as amended).

The Hoeffler et al. reference teaches a method of screening for protein-protein interactions using yeast expression vectors encoding libraries of single chain antibodies. The expression vectors comprise a first nucleotide sequence encoding either  $V_H$  or  $V_L$  subunit, a second nucleotide sequence encoding either  $V_L$  or  $V_H$  subunit, and a peptide linker that connects

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the two subunits. The single chain antibody libraries are comprehensive populations of  $V_L$  and  $V_H$  subunits (vary independently from one another) linked by short, flexible peptide linkers. The reference presents an invention that can probe an animal's entire repertoire of  $> 10^{12}$  combinations of light and heavy variable chains. The Hoeffler et al. reference states that there is a limitation to the diversity of libraries made that is imposed by transformation efficiency not much greater than  $10^7$ . The reference in no way implies that libraries of greater diversity are not desired. The source of DNA for generating the single chain antibody expression vectors may be from immunized or non-immunized animals including humans and mice and from tissues including spleen cells and lymphoblastoid cells. The use of transcriptional activators such as GAL4 are taught.

It would have been obvious to anyone of ordinary skill in the art at the time that the invention was made to use the two-hybrid assay system of Nandabalan et al. with the single chain antibody expression library of Hoeffler et al. Motivation for this combination is found in the Hoeffler et al. reference on pages 1-4 and 37-43. The screening of single chain antibodies in the two-hybrid expression system allows the rapid identification of antibody-antigen pairs. This motivation extends to the screening of any two-subunit proteins, such as receptors and transcription factors in which altering the combinations of subunits produces molecules with different functions.

The Gietz et al. reference teaches methods that allowed the authors to screen a yeast cell library of  $5.2 \times 10^7$  transformants (page 266). The reference teaches that one may make libraries "of  $1 \times 10^6$  independent clones **or more**." It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use the methods of Gietz et al. to optimize the method of Hoeffler et al. One would have been motivated to do this because doing so would increase the proportion of an antibody repertoire that could be screened. One would have had reasonable expectation for success because Gietz et al. had already produced large libraries in yeast for a 2-hybrid screen.

12. Claims 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeffler et al. (1999, WO 99/28502) and Goodman and Gillman's "The Pharmacological Basis of Therapeutics," 9<sup>th</sup> ed. McGraw Hill Publishing (1996) pp. 1365-1386.

The Hoeffler et al. reference teaches a yeast two-hybrid method of screening for protein-protein interactions using yeast expression vectors encoding libraries of single chain antibodies. The expression vectors comprise a first nucleotide sequence encoding either V<sub>H</sub> or V<sub>L</sub> subunit, a second nucleotide sequence encoding either V<sub>L</sub> or V<sub>H</sub> subunit, and a peptide linker that connects the two subunits. The yeast strains used can be diploid or haploid and may be mated (page 22, lines 21-24). The use of  $\alpha$  and  $\bar{a}$  strains of haploid yeast for mating is the most common method of yeast mating. The source of DNA for generating the single chain antibody expression vectors may be from immunized or non-immunized animals including humans and mice and from tissues including spleen cells and lymphoblastoid cells (page 32, lines 5-10). Vectors encoding activating or DNA binding domains of transcriptional activators are taught on page 5. Transcriptional activators such as GAL4 are taught on page 12.

The Hoeffler et al. reference does not teach human growth factor receptor as a specific target protein.

Goodman and Gillman teach that there are diseases related to growth hormone deficiency and over production and that effects of growth hormone are mediated by the growth hormone receptor.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use the method of Hoeffler et al. to identify scFvs that bind to growth hormone receptor that would act as agonists or antagonists of the receptor. One would have been motivated to do so because Hoeffler et al. teach that the scFvs can be used therapeutically and Goodman and Gillman indicate disease states that can be treated by growth hormone receptor agonists and antagonists. One would have had a reasonable expectation for success because the yeast two-hybrid system had been used successfully to find scFvs that bind to target proteins.

13. Claims 18, 19, and 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeffler et al. (1999, WO 99/28502) and Terret, N.K. "Combinatorial Chemistry," Oxford University Press (1998) pp.2-4.

The Hoeffler et al. reference teaches a yeast two-hybrid method of screening for protein-protein interactions using yeast expression vectors encoding libraries of single chain antibodies. The expression vectors comprise a first nucleotide sequence encoding either V<sub>H</sub> or V<sub>L</sub> subunit, a

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second nucleotide sequence encoding either V<sub>L</sub> or V<sub>H</sub> subunit, and a peptide linker that connects the two subunits. The yeast strains used can be diploid or haploid and may be mated (page 22, lines 21-24). The use of  $\alpha$  and  $a$  strains of haploid yeast for mating is the most common method of yeast mating. The source of DNA for generating the single chain antibody expression vectors may be from immunized or non-immunized animals including humans and mice and from tissues including spleen cells and lymphoblastoid cells (page 32, lines 5-10). Vectors encoding activating or DNA binding domains of transcriptional activators are taught on page 5. Transcriptional activators such as GAL4 are taught on page 12.

The Hoeffler et al. reference does not explicitly teach forming a library of mutagenized expression vectors.

The Terret reference teaches the general method of drug discovery including lead discovery and optimization of lead molecules. It would have been obvious to one of ordinary skill in the art at the time that the invention was made to generate a library of mutated expression vectors by standard means such as site directed mutagenesis or DNA shuffling and to screen the mutated library for tester proteins with improved binding affinity for a target. One would have been motivated to do so because optimizing binding of the tester protein with a target protein would lead to the development of tester proteins with greater therapeutic potential. One would have had reasonable expectation for success because mutagenesis, screening, and lead optimization were all standard techniques at the time.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,


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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas Prasthofer** at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

  
DR. JYOTHSNA VENKAT PH.D  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600

Thomas Prasthofer, Ph.D.

October 6, 2001